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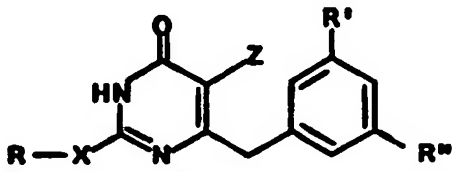
(54) Title: SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

Substituted 6-benzyl-4-oxopyrimidines having formula (I) are described, wherein: X is selected from the group consisting of O and S; R is selected from the group consisting of C_{1-4} alkyl and C_{5-6} cycloalkyl; R', R" and Z, equal or different among them mean H or C_{1-4} alkyl considering that, when X = O, R and R' cannot be both equal to H; their pharmaceutically acceptable salts and their soluble derivatives; one of their preparation processes and their use for the preparation of pharmaceutical compositions useful for the treatment of viral infections.



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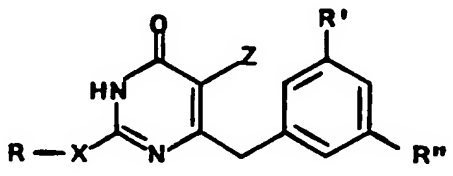
SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

FIELD OF THE INVENTION

The present invention refers to compounds having general formula (I):



(I)

wherein:

X is selected from the group consisting of O and S;

R is selected from the group consisting of C_{1-4} alkyl and C_{5-6} cycloalkyl;

R', R" and Z, equal or different among them mean H or C_{1-4} alkyl considering that, when X=O, R and R' can not be both equal to H; their pharmaceutically acceptable salts and their soluble derivatives;

one of their preparation processes and their use for the preparation of pharmaceutical compositions useful for the treatment of viral infections, particularly of immunodeficiency virus (HIV) infections.

PRIOR ART

The pandemic diffusion of the acquired immunodeficiency syndrome (AIDS) makes urgent the development of chemotherapeutic agents able to halt the replication of the two retroviruses responsible for the infection:

HIV-1 and HIV-2.

Among the various phases characterizing the replication cycle of these viruses the transcription phase of the viral genome (a single RNA filament) in double strand DNA is the most studied one.

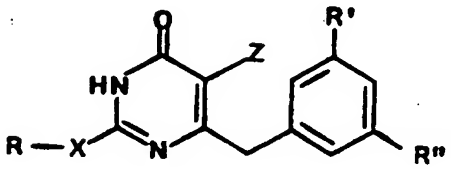
Such a phase, taking place early after the infection, is catalyzed by virus specific enzyme, the reverse transcriptase (RT). The products of pharmaceutical interest able to inhibit the RT may be essentially divided into two classes: nucleosides analogues and non-nucleoside compounds. The four drugs used until now in the AIDS therapy, i.e. AZT, ddI, dhT and ddC, belong to the first class. Other molecules having very different chemical structure, some of which are undergoing clinical trials, belong to the second one. The 3.4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABO) structurally similar to the compounds according to the present invention and having antiviral properties are described in Antiviral Chemistry and Chemotherapy (1993) 4(6), pp. 361-368. Unfortunately the clinical experience has pointed out two major limits of the therapy with said antivirals.

Following chronical treatment, on the one hand collateral toxicity phenomena appear (remarkable in the case of the nucleosides analogous). On the other hand, drug-resistant mutants appear (very quickly in the case of non-nucleoside RT inhibitors). It is therefore evident the necessity to have available always new molecules active and useful in this field of application.

DETAILED DESCRIPTION OF THE INVENTION

The present invention allows to overcome the above mentioned drawbacks

by compounds having general formula (I)



(I)

wherein:

X is selected from the group consisting of O and S;

R is selected from the group consisting of C_{1-4} alkyl and C_{3-6} cycloalkyl;

R', R" and Z, equal or different among them mean or C_{1-4} alkyl considering that, when X=O, R and R' can not be both equal to H;

their pharmacologically acceptable salts and their soluble derivatives.

As it can be noticed, the compounds of the present invention differ from the DABO described in the above reported literature owing to the presence of one S atom in the place of the O atom or owing to the presence of substituents on the benzylic ring. In Tables 3 and 4 the activity of some compounds according to the invention is reported, while in the Table 5 the data obtained with the above mentioned DABO compounds are reported by comparison. In the light of the biological activity data, the products having formula (I) wherein:

X = O, Z = H, R = cyclohexyl, R' = CH_3, R" = H

X = O, Z = H, R = cyclohexyl, R' = CH_3, R" = CH_3

X= O, Z = CH_3, R = sec-butyl, R' = CH_3, R" = CH_3

X = S, Z = H, R = iso-propyl, R' = CH_3, R" = H

X = S, Z = H, R = sec-butyl, R' = CH_3, R" = H

X = S, Z = H, R = cyclopentyl, R' = CH_3, R" = H

X = S, Z = CH_3, R = methyl, R' = H , R" = H

X = S, Z = CH_3, R = cyclopentyl, R' = H , R" = H

X = S, Z = CH_3, R = cyclohexyl, R' = H , R" = H

X = S, Z = CH_3, R = cyclopentyl, R' = CH_3, R" = H

X = S, Z = CH_3, R = cyclopentyl, R' = CH_3, R" = H

turned out to be particularly interesting.

PREPARATION OF THE COMPOUNDS HAVING FORMULA (I) WHEREIN X = S (see scheme "A")

Thiourea (43 mmol) and the suitable methyl phenylacetylacetate (31.5 mmol) are added to a solution of sodium methoxide obtained dissolving metallic sodium (0.063 g-atoms) in anhydrous methanol (50 ml) and the resulting mixture is left to reflux under magnetic agitation for 5 hours. After cooling the solvent is evaporated at reduced pressure, the residue is taken back with water (200 ml) and the mixture is acidified to pH 5 with 0.5 N acetic acid and extracted with ethyl acetate (3 x 100 ml).

The solid in case separated (raw 2-thiouracil) is vacuum filtered, stove dried and crystallized by a suitable solvent while the reunited organic extracts are washed with a saturated solution of NaCl (2 x 100 ml), dried (Na_2SO_4) and concentrated at reduced pressure to give the 2-thio(5-alkyl)-6-benzyl(substituted)uracil (1).

Subsequently, according to the method A, methyl iodide (8 mmol; 1.13 g) is added to a solution containing the suitable 2-thiouracil derivative

(4 mmol) dissolved in anhydrous N,N-dimethylformamide (2 ml) and the mixture is left under agitation at room temperature until the starting material disappears by the thin-layer chromatography check (silica gel/n-hexane: ethyl acetate: methanol 12:3:1). Subsequently the solution is diluted with water (200 ml), the aqueous phase is extracted with ethyl acetate (3 x 50 ml) and the reunited organic extracts are washed with a solution saturated with sodium thiosulfate (100 ml), with a solution saturated with NaCl (100 ml), dried (Na_2SO_4) and deprived of the solvent.

The 3,4-dihydro-2-methylthio-(5-alkyl)-6-benzyl(substituted)-4-oxopyrimidine derivatives (2) so obtained are then purified by a suitable solvent.

Alternatively, according to the methods B and C, anhydrous potassium carbonate (4.2 mmol) and the suitable alkyl halide (4.4 mmol) are added to a solution containing the suitable 2-thiouracil derivative (4 ml) dissolved in anhydrous N,N-dimethylformamide (2 ml) and the resulting mixture is left under agitation at room temperature (method B) or at 80 °C (method C) until the starting material disappears by the thin-layer chromatography check (silica gel/n-hexane: ethyl acetate: methanol 12:3:1).

Subsequently the solution is diluted with water (200 ml), it is acidified to pH 5 with 0.5 N acetic acid and the aqueous phase is extracted with ethyl acetate (3 x 50 ml). The reunited organic extracts are washed with a saturated solution of sodium thiosulfate (100ml), with a saturated solution of NaCl (100 ml), dried (Na_2SO_4) and

concentrated at reduced pressure.

The 3,4-dihydro-2-alkylthio-(5-alkyl)-6-benzyl (substituted)-4-oxopyrimidine derivatives (3) and (4) so obtained are then purified by crystallization from a suitable solvent or by chromatography (silica gel/n-hexane: ethyl acetate: methanol 12:3:1). The physico-chemical data of some of the obtained products are reported in the Table 1.

PREPARATION OF THE COMPOUNDS HAVING GENERAL FORMULA (I) WHEREIN Y = O (see scheme B)

$SOCl_2$ (21.3 ml) is slowly added under nitrogen atmosphere to the suitable phenylacetic acid (43.2 mmol) and the resulting solution has been warmed for 2 hours. After cooling the solvent has been dried at reduced pressure.

A solution of the raw 3'-methyl or 3',5'-dimethyl phenylacetyl chloride (160 mmol) so obtained in 50 ml of anhydrous CH_2Cl_2 has been added in 2 hours, at 0 °C and under nitrogen atmosphere, to a suspension of 23.75 g (165 mmol) of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum acid) in 65 ml of anhydrous CH_2Cl_2 containing 32.5 ml (400 mmol) of anhydrous pyridine, under strong agitation. The agitation has been continued for 1 hour at 0 °C and for a further hour at room temperature, then the mixture has been poured on ice and treated with 2N HCl. The organic layer has been picked up and the aqueous solution washed two times with CH_2Cl_2. The organic phase and the extracts have been reunited, washed with brine and dried.

The evaporation of the solvent under reduced pressure gave the acylated product 5 as a brown solid which has been put to reflux in 200 ml of

CH_3OH for 20 hours.

After vacuum evaporation of the solvent and chromatographic purification the compounds 6 are respectively obtained.

Metallic sodium (3.68 g) is added to a solution of the above mentioned compounds 6 in methanol (250 ml) and the solution is stirred to complete dissolution of the metal. CH_3I is dropped in the solution and the resulting mixture is reflux warmed for 4 hours.

After cooling the solvent has been removed and the residue has been treated with H_2O (200 ml) and extracted with $CHCl_3$ (3 x 100 ml). The organic layer has been washed with brine (2 x 100 ml), dried and evaporated to give a residue which, purified by chromatography, has given the compounds 7 as a yellow oil.

A solution of the compounds 6 or 7 (10 mmol) in CH_3OH (50 ml) has been added to a suspension of O-methylisourea hydrogensulfate (15 mol) and $Ca(OH)_2$ (16 mmol) under strong agitation. The resulting mixture has been stirred at room temperature for 72 hours and then concentrated, acidified to pH 5 with 0.5 N acetic acid and extracted with ethyl acetate (3 x 50 ml). The organic extracts have been washed with brine (100 ml), dried and dry evaporated. The residue, purified by crystallization from a suitable solvent gave the pure compounds 8.

Metallic potassium (100 mmol) in small pieces has been slowly added under agitation to the suitable alcohol (200 ml) freshly distilled on sodium. The dissolution of the metal has been completed by warming the mixture at 70-80 °C and then the derivatives 8 (10 mmol) are added and the obtained mixture is reflux warmed under nitrogen atmosphere. The

reaction has been stopped when the chromatographic check confirmed the disappearance of the starting 4-pyrimidone.

The mixture has been diluted with water (100 ml) after cooling, acidified to pH 5 with 0.5 N acetic acid and extracted with ethyl acetate (3 x 50 ml).

The reunited extracts have been washed with brine (100 ml), dried and evaporated to give the raw products 9 which have been purified by column chromatography and crystallized again by a suitable solvent.

In some cases the methoxy group in the position 2 of the compounds 8 wherein R = R_2 = H, R_1 = CH_3 or R = R_1 = R_2 = CH_3 has been removed with formation of the respective compounds 10 wherein R = R_1 = H, R_2 = CH_3 and R = R_1 = R_2 = CH_3 as collateral products.

The physico-chemical data of some of the obtained products are reported in the Table 2.

The products obtained acting as above described with the relative data of cytotoxicity and anti-HIV 1 activity are reported in the Tables 3 and 4.

BIOLOGICAL ACTIVITY

In order to illustrate the activity of the compounds in the HIV-1 infections the results in vitro are reported relating to:

- cytotoxicity for different cell lines and bone marrow cells from HIV seronegative subjects;
- inhibitory activity with regard to HIV-1;
- capability to inhibit the reverse transcriptase of HIV-1 in tests with recombinant enzyme (rRT) of HIV-1.

The cells used in this study were MT-4 and C8166, both T4 lymphocytes lines permissive for the HIV replication. The cells were suspended in RPMI 1640 added with fetal calf serum (FCS) at 10%, penicillin 100 U/ml and streptomycin 100 µg/ml.

The cell cultures were incubated at 37 °C in 5% CO_2 atmosphere and were periodically checked to verify the absence of mycoplasmas contamination.

For the evaluation of the compounds cytotoxicity a colorimetric method has been employed based on the use of a tetrazolium salt, the 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium-bromide (MTT), which is transformed by the mitocondrial enzyme succinic dehydrogenase into a blue coloured product, the formazane, the amount of which turns out to be directly proportional to the number of viable cells.

In short 50 µl of RPMI containing 1 x 10^4 cells (MT-4, C8166, U937, PBL) were added, in 96 wells multiplates, to 50 µl of RPMI containing or not scalar dilutions of the compounds under examination. After 4 days of incubation at 37 °C 20 µl of MTT (2.5 µg/ml) have been added to each well. After 4 hours of incubation at 37 °C the produced formazane was solubilized by adding 150 µl/well of an isopropanol solution containing 0.34% of HCl and 5% of Nonidet P40 (NP-40), a non-ionic detergent.

The amount of formazane was then determined at the spectrophotometer by evaluation of the optical density at 570 nm. The values shown in the columns CC_{50} represent the compound concentrations required to reduce by 50% the MTT metabolization and, therefore, the cell viability; the

mitocondrial metabolic process is, in fact, in a linear relation with the cell viability. As it is shown in the Tables, the major part of the compounds has low or null cytotoxicity in non infected cells, even at the maximum concentrations tested. The inhibition of the virus-induced cytopathogenicity constituted the estimation criterion of the anti-HIV-1 activity of the compounds.

The virus used in the antiviral tests (HIV-1, strain III_B has been obtained from the chronically infected $H9/III_B$ cells supernatant. The virus stock solutions were titled in C8166 and mantained at -80 °C till the moment of use. MT-4 cells, seeded at a density equal to 3×10^6/ml, were infected with HIV-1 at a multiplicity of infection (m.o.i.) equal to 0.01. After 1 hour of incubation at 20 °C and subsequent removal of the inoculum, the cells were washed three times and then suspended again at a density equal to 1×10^5/ml, in absence or in presence of the test compounds.

After 4 days of incubation at 37 °C the cell survival was determined with the above mentioned MTT method, in order to compute the values of EC_{50} representing the compound concentration necessary to reduce by 50% the virus-induced cytopathogenicity.

The results reported in the Tables show that the test compounds are active in inhibiting the HIV-1 multiplication in MT-4 cells. They, owing to the lack of citotoxicity, have a selectivity index (meant as ratio between cytotoxicity and anti-HIV activity) particularly favourable.

In order to complete the antiviral activity analysis of the compounds

we proceeded to estimate the effects of the interaction of the various molecules with the target enzyme, the reverse transcriptase (RT). The gene of this enzyme has been formerly cloned in an expression vector, the protein has been expressed in E.coli and subsequently has been purified to obtain a preparation with a high purity degree. The tests with the recombinant RT (rRT) have been carried out at 37 °C for 30 minutes in 50 µl containing 50 mM tris-HCl (pH 7.8), 1 mM dithiotreitol, 80 mM KCl, 6 mM $MgCl_2$, 0.1 mg/ml bovine serum albumin, 10 µM [^{3}H]-dTTP (1Ci/mmol) or [^{3}H]-dGTP (1 Ci/mmol), 0.05 OD_{260} units/ml of Poly(rC)-oligo$(dG)_{12-18}$ and 0.002 units of enzyme. A unit is defined as the amount of enzyme necessary to incorporate 1 nmol of [^{3}H]-dTTP in the "template-primer" Poly(rA)-oligo$(dT)_{10}$ in one minute at 37 °C. After incubation, 40 µl of the reaction have been transferred on Whatman GF/A glass fiber filters and processed for the determination of the acid insoluble radioactivity after treatment with trichloroacetic acid. The values reported in the Tables (IC_{50}) represent the compound concentration required to reduce the enzyme activity by 50%.

The analysis of the values of IC_{50} reveals a good correlation with the values of EC_{50} confirming that the specific target of the compounds object of the invention is the reverse transcriptase.

SCHEME "A"

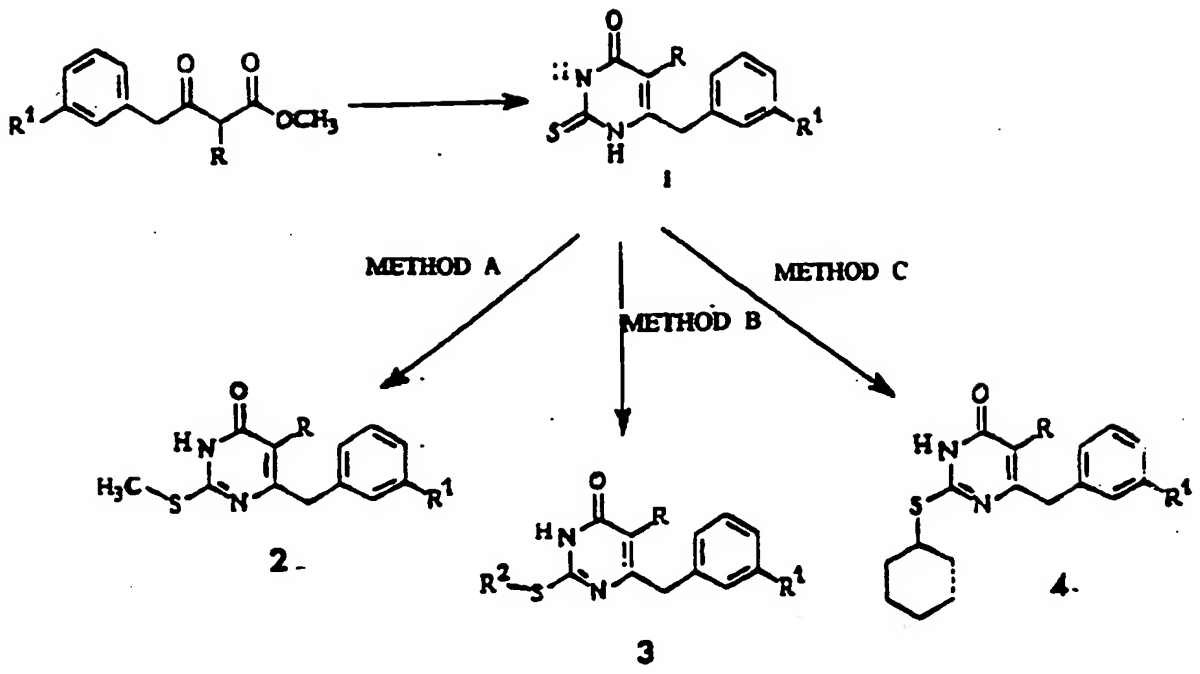


TABLE 1

Physico-chemical characteristics of the compounds 2,3,4 according to the scheme "A"

Comp.	R	R^1	R^2	m.p.(°C)	solv.of cryst.	yield
2	H	H	methyl	183-184	benzene	98
2	H	Me	methyl	159.5-160.0	benzene	94
2	Me	H	methyl	199-200	benzene	98
2	Me	Me	methyl	195-196	benz./cyclohex.	97
3	H	H	iso-propyl	123.5-124.5	cyclohexane	97
3	H	H	iso-butyl	131.5-132.5	cyclohexane	90
3	H	H	sec-butyl	100-102	cyclohexane	82
3	H	H	cyclopentyl	147-148	cyclohexane	84
3	H	Me	iso-propyl	122-123	cyclohexane	86
3	H	Me	iso-butyl	111-112	n-hexane	78
3	H	Me	sec-butyl	76-78	n-hexane	69
3	H	Me	cyclopentyl	157-158	benz./cyclohex.	76
3	Me	H	iso-propyl	150-151	cyclohexane	95
3	Me	H	iso-butyl	114.5-115.0	n-hexane	92
3	Me	H	sec-butyl	127.5-128.0	n-hexane	90
3	Me	H	cyclopentyl	166-167	cyclohexane	85
3	Me	Me	iso-propyl	135-136	cyclohexane	94
3	Me	Me	iso-butyl	110.5-111.0	n-hexane	90
3	Me	Me	sec-butyl	121-122	n-hexane	82
3	Me	Me	cyclopentyl	169-170	cyclohexane	89
4	H	H	cyclohexyl	172-173	benz.-cyclohex.	72
4	H	Me	cyclohexyl	177-178	benz.-cyclohex.	68
4	Me	H	cyclohexyl	180-182	benz.-cyclohex.	70
4	Me	Me	cyclohexyl	179-180	benz.-cyclohex.	62

SCHEME "B"

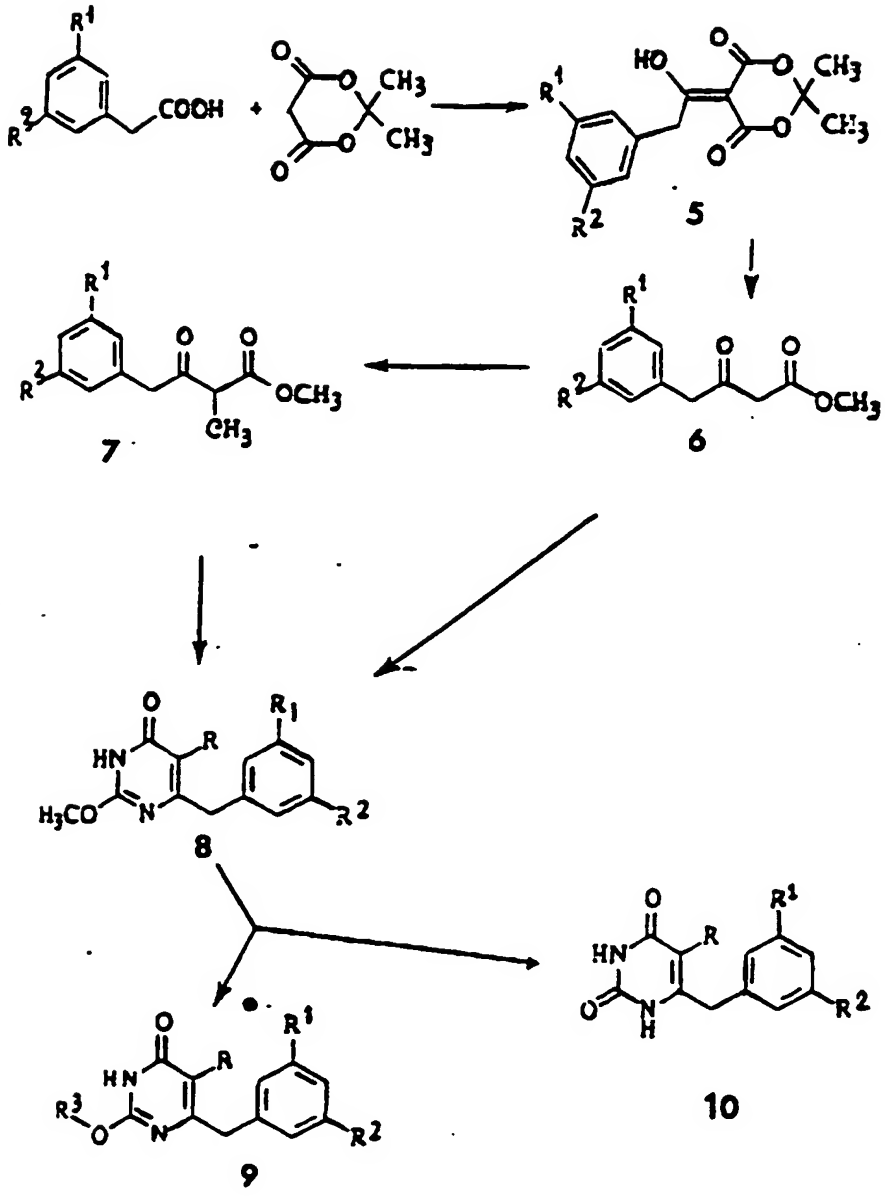


TABLE 2

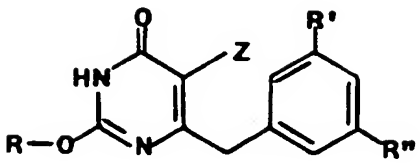
Physico-chemical characteristics of the compounds 9 according to the scheme "B"

R	R^1	R^2	R^3	m.p. (°C)	yield	chromat. syst.a	Cryst. solv.b
H	CH_3	H	iso-propyl	124-126	22	B	E/G
H	CH_3	H	sec-butyl	144-145	35	B	E
H	CH_3	H	iso-butyl	92-93	16	B	E
H	CH_3	H	cyclo-pentyl	129-131	24	B	H/G
H	CH_3	H	cyclo-hexyl	150-151	20	B	F
CH_3	CH_3	H	iso-propyl	200-204	18	B	E
CH_3	CH_3	H	sec-butyl	123-124	24	B	H
CH_3	CH_3	H	iso-butyl	110-112	12	B	D
CH_3	CH_3	H	cyclo-pentyl	198-199	20	B	H
CH_3	CH_3	H	cyclo-hexyl	210-211	26	B	G
H	CH_3	CH_3	iso-propyl	162-164	26	B	E
H	CH_3	CH_3	sec-butyl	166-167	32	B	E
H	CH_3	CH_3	iso-butyl	115-116	20	B	G
H	CH_3	CH_3	cyclo-pentyl	173-176	28	B	C
H	CH_3	CH_3	cyclo-hexyl	187-189	28	B	H/E
CH_3	CH_3	CH_3	sec-butyl	158-159	22	B	E
CH_3	CH_3	CH_3	iso-butyl	163-165	32	B	E
CH_3	CH_3	CH_3	cyclo-pentyl	189-190	18	B	E
CH_3	CH_3	CH_3	cyclo-hexyl	227-228	20	B	E

[a] A = silica gel/chloroform; B = silica gel/ethyl acetate:chloroform (1:2)

[b] C = ethanol; D = ethyl acetate; E = cyclohexane; F = n-hexane; G = petroleum ether; H = benzene.

TABLE 3



Substituents				[μM]			
Z	R	R'	R''	[a] CC_{50}	[b] EC_{50}	[c] IC_{50}	[d] S.I.
H	H	CH_3	H	>463	92	>10	5
H	methyl	CH_3	H	>434	108	>10	>4
H	iso-propyl	CH_3	H	263	6.5	1.0	40
H	sec-butyl	CH_3	H	132	1.8	-	73
H	iso-butyl	CH_3	H	>367	3.3	2.0	>111
H	cyclo-pentyl	CH_3	H	352	2.8	3.1	125
H	cyclo-hexyl	CH_3	H	>335	0.8	1.8	>41
H	H	CH_3	CH_3	-	-	-	-
H	methyl	CH_3	CH_3	>410	34.4	>10	>2
H	iso-propyl	CH_3	CH_3	>367	3.1	3.2	>118
H	sec-butyl	CH_3	CH_3	104	1.4	1.0	74
H	iso-butyl	CH_3	CH_3	>349	2.7	3.4	>129
H	cyclo-pentyl	CH_3	CH_3	>335	3.3	3.0	>100
H	cyclo-hexyl	CH_3	CH_3	>320	1.1	1.0	>291
CH_3	H	CH_3	H	-	-	-	-
CH_3	methyl	CH_3	H	381	>381	-	-
CH_3	iso-propyl	CH_3	H	>367	>367	-	-
CH_3	sec-butyl	CH_3	H	210	4.6	-	46
CH_3	iso-butyl	CH_3	H	>350	3.1	2.1	>113
CH_3	cyclo-pentyl	CH_3	H	335	56.3	-	6
CH_3	cyclo-hexyl	CH_3	H	>330	16.7	1.7	>19
CH_3	H	CH_3	CH_3	>410	38	-	>11
CH_3	methyl	CH_3	CH_3	>387	>387	-	-
CH_3	iso-propyl	CH_3	CH_3	-	-	-	-
CH_3	sec-butyl	CH_3	CH_3	>333	0.8	-	>416
CH_3	iso-butyl	CH_3	CH_3	77	40	-	2
CH_3	cyclo-pentyl	CH_3	CH_3	>320	29	-	>11
H	cyclo-hexyl	CH_3	CH_3	>307	14	-	>22

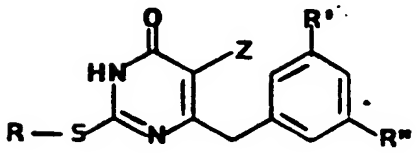
[a] Compound dose required to reduce the number of viable cells by 50%, as determined by the MTT method;

[b] Compound dose required to protect 50% of MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method;

[c] Compound dose required to inhibit the rRT HIV-1 activity by 50%;

[d] Selectivity index, CC_{50}/EC_{50} ratio.

TABLE 4



Substituents				[μM]			
Z	R	R'	R''	[a]CC_{50}	[b]EC_{50}	[c]IC_{50}	[d]S.I.
H	methyl	H	H	>431	34.5	>10	12
H	iso-propyl	H	H	332	7.7	3.0	43
H	sec-butyl	H	H	150	1.2	1.7	125
H	iso-butyl	H	H	186	5.1	3.4	36
H	cyclo-pentyl	H	H	147	1.7	2.8	86
H	cyclo-hexyl	H	H	>330	0.8	3.0	>412
H	H	CH_3	H	258	>258	>10	-
H	methyl	CH_3	H	317	17	6.7	19
H	iso-propyl	CH_3	H	>310	1.3	0.9	>238
H	sec-butyl	CH_3	H	>347	0.54	1.2	>642
H	iso-butyl	CH_3	H	>347	12.5	1.4	>28
H	cyclo-pentyl	CH_3	H	>333	1.2	2.6	>278
H	cyclo-hexyl	CH_3	H	87	3	3.6	29
CH_3	H	H	H	431	108	10	-
CH_3	methyl	H	H	>406	1.2	4.9	>338
CH_3	iso-propyl	H	H	140	1.8	1.5	77
CH_3	sec-butyl	H	H	86	0.6	2.4	140
CH_3	iso-butyl	H	H	62	0.8	2.2	78
CH_3	cyclo-pentyl	H	H	166	0.6	3.4	270
CH_3	cyclo-hexyl	H	H	>318	0.6	4.3	>530
CH_3	H	CH_3	H	284	>102	>10	-
CH_3	methyl	CH_3	H	385	3.0	2.5	128
CH_3	iso-propyl	CH_3	H	100	1.3	2.5	77
CH_3	sec-butyl	CH_3	H	100	1.0	2.7	100
CH_3	iso-butyl	CH_3	H	100	1.6	4.6	62
CH_3	cyclo-pentyl	CH_3	H	>318	0.6	4.4	>530
CH_3	cyclo-hexyl	CH_3	H	>304	0.6	0.3	>506

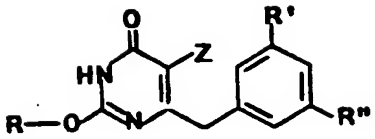
[a] Compound dose required to reduce the viability of the MT-4 cells by 50%, as determined by the MTT method;

[b] Compound dose required to protect 50% of the MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method;

[c] Compound dose required to inhibit by 50% the rRT HIV-1 activity;

[d] Selectivity index, CC_{50}/EC_{50} ratio.

TABLE 5



Substituents				[μM]			
Z	R	R'	R''	$^{a}CC_{50}$	$^{b}EC_{50}$	$^{c}IC_{50}$	$^{d}S.I.$
H	H	H	H	>1000	>200	>10	-
H	methyl	H	H	>1000	>200	>10	-
H	iso-propyl	H	H	646	26	5.5	25
H	sec-butyl	H	H	344	5.5	4.2	62
H	iso-butyl	H	H	-	-	-	-
H	cyclo-pentyl	H	H	466	41	>10	11
H	cyclo-hexyl	H	H	157	9.0	>10	17
CH_3	H	H	H	>1000	>200	-	-
CH_3	methyl	H	H	517	>200	-	-
CH_3	iso-propyl	H	H	243	16	-	15
CH_3	sec-butyl	H	H	180	2.9	-	63
CH_3	cyclo-pentyl	H	H	>1000	10	-	>100
CH_3	cyclo-hexyl	H	H	375	4.7	-	80

[a] Compound dose required to reduce the viability of the MT-4 cells by 50%, as determined by the MTT method;

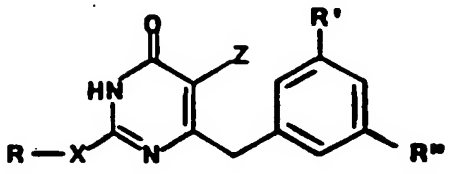
[b] Compound dose required to protect 50% of the MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method;

[c] Compound dose required to inhibit by 50% the rRT HIV-1 activity;

[d] Selectivity index, CC_{50}/EC_{50} ratio.

CLAIMS

1. Compounds having general formula (I)



(I)

wherein:

X is selected from the group consisting of O and S;

R is selected from the group consisting of C_{1-4} alkyl and C_{5-6} cycloalkyl;

R', R" and Z, equal or different among them, mean H or C_{1-4} alkyl considering that, when X=O, R and R' can not be both equal to H;

their pharmaceutically acceptable salts and their soluble derivatives.

2. Compounds having general formula (I) as claimed in claim 1 wherein X=S.

3. Compounds having general formula (I) as claimed in claim 1 wherein:

X = O, Z = H, R = cyclohexyl, R' = CH_3, R" = H

X = O, Z = H, R = cyclohexyl, R' = CH_3, R" = CH_3

X= O, Z = CH_3, R = sec-butyl, R' = CH_3, R" = CH_3

X = S, Z = H, R = iso-propyl, R' = CH_3, R" = H

X = S, Z = H, R = sec-butyl, R' = CH_3, R" = H

X = S, Z = H, R = cyclopentyl, R' = CH_3, R" = H

8 X = S, Z = CH_3, R = methyl, R' = H , R" = H

9 X = S, Z = CH_3, R = cyclopentyl, R' = H , R" = H

10 X = S, Z = CH_3, R = cyclohexyl, R' = H , R" = H

11 X = S, Z = CH_3, R = cyclopentyl, R' = CH_3, R" = H

12 X = S, Z = CH_3, R = cyclopentyl, R' = CH_3, R" = H

1 4. Process for the preparation of the compounds having formula (I) as
2 claimed in claim 1 wherein X = S, wherein: the suitable methyl
3 phenylacetylacetate is reacted with thiourea in presence of sodium
4 methoxide and the so obtained 2-thio(5-alkyl)-6-benzyl
5 (substituted)uracils are reacted with methyl iodide, or with an alkyl
6 halide in a basic medium.

1 5. Process for the preparation of the compounds having formula (I) as
2 claimed in claim 1 wherein X = O, wherein: a 3'-methyl or 3',5'-
3 dimethylphenylacetyl chloride is reacted with 2,2-dimethyl-1,3-dioxane-
4 4,6-dione, the so obtained compound is reacted with CH_3I, the so
5 obtained compound (or its precursor) is reacted with O-methyl isourea
6 hydrogensulfate and the obtained product is reacted with the suitable
7 potassium alcoholate.

1 6. Use of the products as claimed in claim 1 for the preparation of
2 pharmaceutical compositions having antiviral activity.

1 7. Use as claimed in claim 6 wherein the antiviral activity is an anti-
2 HIV activity.

1 8. Use as claimed in claim 7 wherein the anti-HIV activity is an anti-
2 HIV-1 activity.

9. A therapeutic method for treating viral infections consisting of the administering to a patient in need thereof a therapeutically effective amount of at least one compound having formula (I) according to claim 1.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 95/03912

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/52 A61K31/505 C07D239/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 18887 (SMITH-KLINE) 12 December 1991 see page 24; claims	1,2
A	EP,A,0 123 402 (FUJISAWA) 31 October 1984 see claims	1-8
P,X	CHEMICAL ABSTRACTS, vol. 122, no. 1, 1995, Columbus, Ohio, US; abstract no. 122513c, S.MASSA,A.MAI 'SYNTHESIS AND ANTIVIRAL ACTIVITY OF 3,4-DIHYDRO-2-ALKOXY-6-BENZYL-4-OXOPYRIMIDINES' page 23 ; see abstract	1-8
P,X	& ANTIVIRAL CHEM. CHEMOTHER., vol.6, no.1, 1995, ENGL. pages 1 - 8	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 1996	16.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 95/03912

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol.38, no.17, 18 August 1995, WASHINGTON US pages 3258 - 3263 A.MAI ET AL. 'SYNTHESIS AND ANTI-HIV-1 ACTIVITY OF THIO ANALOGUES OF DIHYDROALKOXYBENZYLOXOPYRIMIDINES.' see page 3258 - page 3262	1-8

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/03912

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 9 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the attributed effects of the compounds (Rule 39.1.(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 95/03912

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9118887	12-12-91	AU-B-	7971691	31-12-91
EP-A-0123402	31-10-84	AU-B-	564793	27-08-87
		AU-B-	2587484	27-09-84
		CA-A-	1256107	20-06-89
		DE-A-	3473875	13-10-88
		JP-A-	59181265	15-10-84
		JP-C-	1835761	11-04-94
		JP-A-	62270563	24-11-87
		SU-A-	1349698	30-10-87
		SU-A-	1436872	07-11-88
		US-A-	4824851	25-04-89
		US-A-	4612376	16-09-86
		US-A-	4746664	24-05-88